Annexin V C/T-1 polymorphism and pregnancy complications

The –1T variant of the annexin V gene, which has been suggested to have a protective role against thrombotic disease, was evaluated in 140 women with pregnancy complications and 317 control women with uncomplicated pregnancies. The presence of the -1 CT or TT genotype did not show a protective effect in normal pregnancies.

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Pregnancy complications such as intrauterine growth restriction (IUGR), pre-eclampsia, *abruptio placentae* and late fetal loss are often associated with abnormal placental development and disturbances of hemostasis leading to inadequate placental perfusion. The human placental syncytiotrophoblast is a rich source of annexin V, a protein that displays a strong *in vitro* anticoagulant activity due to its high affinity binding to negatively charged phospholipids and to its capacity to displace coagulation factors from phospholipid membranes, creating a protective shield against procoagulant reactions. The anatomic location of annexin V on the apical surface of placental villi facing the maternal slow-moving blood in the intervillous circulation might, therefore, play an antithrombotic role by inhibiting intervillous thrombosis and maintaining blood fluidity, so that nutrition exchange functions in the placenta result unimpaired. It has been reported that pregnant women with anti-phospholipid circulating antibodies and recurrent placental thromboses show decreased levels of annexin V on the placental villi,[1] but these data were not confirmed by others.[2] Recently, a C to T transition has been described in the Kozak region of the annexin V gene, at position –1, directly associated with the regulation of translation.[3] The –1T variant increases translation efficiency, resulting in a 1.4 fold increase in protein production, suggesting a protective role against thrombotic disease, as reported in premature myocardial infarction.[3] Considering that annexin V is highly concentrated in the placenta, we hypothesized that complicated pregnancies such as those with late fetal loss or IUGR may be associated with a reduced expression of annexin V (associated with the -1 CC allele).

One hundred and forty-three women with pregnancy complications (95 with late fetal loss and 48 with IUGR) and 334 control women with uncomplicated pregnancies and no history of thromboembolic diseases were investigated. The characteristics of the study population have been reported elsewhere.[4,5] Briefly, late fetal loss was defined as intrauterine fetal death after 20 weeks of gestation, according to the WHO. IUGR pregnancies were defined by the concomitant presence of three characteristics: reduced intrauterine growth; birth weight below the 10th percentile for birth weight and gestational age, and abnormal Doppler velocimetry of the umbilical artery. Causes for exclusion were: history of venous thrombosis or the presence of anti-phospholipid syndrome, uterine or placental malformations, multiple gestation with late fetal loss of only one fetus, hydrops or erythroblastosis fetalis, congenital anomalies or abnormal karyotyping of the fetus.

Table 1. Prevalence of the -1 CT annexin V polymorphism in cases and controls.

	All patients	*All controls*	*LFL patients*	*Matched LFL controls*	*IUGR patients*	*Matched IUGR controls*
Annexin V -1 CT or TT	30/140 (21%)	75/317 (24%)	14/94 (15%)	50/221 (23%)	16/46 (35%)	25/96 (26%)
Adjusted OR*	OR=0.92 (95%CI 0.57-1.49)		OR=0.65 (95%CI 0.34-1.25)		OR=1.45 (95%CI 0.68-3.10)	

**Adjusted for the presence of factor V Leiden and prothrombin G20210A; LFL: late fetal loss; IUGR: intrauterine growth retardation; OR: odds ratio.*

The –1 CT polymorphism of the annexin V gene was evaluated by polymerase chain reaction amplification and restriction analysis (using Nco I) in 140 cases and 317 controls. The prevalence of the rare genotype (-1 CT or TT) in the control group (24%) was similar to that described by Gonzales-Conejero (22%).[3] The presence of the -1 CT or TT genotype did not show a protective effect in all complicated pregnancies taken together. Nevertheless, when patients with late fetal loss or IUGR were analyzed separately, the prevalence of the –1 CT or TT genotype appeared significantly different (15% and 35% respectively, p=0.02), suggesting that these pregnancy complications might have different pathogenetic mechanisms. However this study did not have sufficient power to analyze late fetal loss and IUGR separately and observe a 2 fold risk reduction associated with the –1 CT or TT genotype in the late fetal loss group. Another drawback of this study is the lack of data regarding a third group of patients affected by pre-eclampsia.

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